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ORIGINAL ARTICLES

Combined inhalation of nitric oxide and oxygen in patients with moderate to severe COPD: effect on blood gases

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Abstract Inhaled nitric oxide (NO) has been reported to improve oxygenation in patients with COPD if administered in combination with oxygen (O_2). Little, however, is known about the variability of these effects and the potential influence of body position. Twenty-six spontaneously breathing patients with moderate to severe COPD inhaled clean air, O_2(FiO_2, 0·29), 5 ppm NO, 5 ppm NO+O_2, 10 ppm NO+O_2, 10 ppm NO, and again clean air in an upright position. Blood gas analysis from arterialized capillary blood was performed after each inhalation. Tests were repeated on different days to assess the variability of the response. Furthermore, eight patients were studied in both upright and supine position while inhaling 5 ppm NO in the presence or absence supplemental O_2. As compared to clean air, NO led to a mean decrease in PaO_2 of −0·9 mmHg at 5 ppm and of−2· 8 mmHg at 10 ppm NO. Similarly, NO+O_2 led to a dose-dependent fall in PaO_2 of −1·8 and −3·6 mmHg, respectively, as compared to O_2. Average within-subject variation (SD) of the effects elicited by 5 and 10 ppm NO was 2·4 and 2·3 mmHg without additional O_2, and 4·7and 5·3 mmHg with O_2. The effects of 5 ppm NO+O_2 differed significantly between upright and supine position; as compared to O_2 alone, mean (SD) changes were −3·7 ±5·8 *vs.* +1·1 ±4·9 mmHg, respectively. Our findings suggest that the addition of NO to inhaled oxygen, when given in an upright position, does not lead to an improvement of PaO_2 in patients with moderate to severe COPD. Furthermore, it turned out that it was not possible to define responders and non-responders to inhaled NO on an individual basis, since the variability of the responses was similar to the mean effect.

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INTRODUCTION

In 1980 Furchgott and Zawadzki revealed that mammalian cells are capable of producing a potent vasodilator which was called endothelium-derived relaxing factor (EDRF) (1). Later studies suggested that EDRF is identical to nitric oxide (NO) (2,3). Therefore the potential effect of the inhalation of NO was studied in a number of diseases involving disorders of vascular tone or ventilation–perfusion mismatching, such as adult respiratory distress syndrome (ARDS) (4), primary pulmonary hypertension (5), pulmonary fibrosis (6) or chronic obstructive pulmonary disease (COPD).

In COPD, hypoxaemia is a common phenomenon, primarily as a consequence of ventilation–perfusion mismatch; there is no evidence on hypoxaemia owing to increased intrapulmonary shunt and diffusion impairment (7). Based on this, it has been suggested that inhalation of vasoactive compounds such as NO might influence the ventilation–perfusion ratio and thereby alter the level of oxygenation.

In one of the initial studies on inhaled NO in COPD, Barberà *et al*. (8) found that breathing of 40 ppm NO led to a worsening of pulmonary gas exchange as indicated by a decrease in arterial oxygen pressure (PaO_2). This was explained by an increase in blood flow through poorly ventilated alveolar units. In contrast, pulmonary artery pressure and pulmonary

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vascular resistance decreased significantly during inhalation of NO.

In accordance with these findings, Yoshida *et al*. (9) reported that inhalation of 2 ppm NO in normoxaemic patients with COPD resulted in a deterioration of PaO_2. If, however, inhalation of NO was combined with that of O_2 (1 O_2 min^{-1}), PaO_2 improved to 111·5 mmHg as compared to 91·4 mmHg after O_2 alone. Similary, German *et al*. (10) investigated the effect of inhaled NO added to long-term oxygen therapy (LTOT). Addition of 5 ppm NO to ongoing LTOT led to a significant increase in PaO_2 but there was no further increase when concentrations were raised to 10 or 20 ppm, thereby indicating a ceiling effect of NO.

Noteworthy, all available data have been obtained with patients in supine or semi-supine position. Since it is known that changes in body position can affect ventilation–perfusion matching (11), the results may not be conferred to the upright position. It might be argued that the clinical usefulness of NO within a long-term treatment depends on the requirement that the therapy is effective during normal daytime activities, which predominantly involve an upright position. Based on these considerations, we studied the effects of the inhalation of NO and oxygen in patients with moderate to severe COPD, when patients were seated during inhalation. Measurements were repeated on a second day to assess the reproducibility of the effects of NO and to identify potential responders and non-responders. We also included a group of patients who were studied in both upright and supine position.

PATIENTS AND METHODS

Study design

Twenty-six spontaneously breathing patients with moderate to severe COPD were included (25 males, one female; mean age, 67±7·5 years; range, 50–79 years; Table 1). The diagnosis of COPD met ERS criteria (12) and all patients showed airflow limitation, with FEV_1 <70% of predicted values and FEV_1/VC ratio <0·7. They were not within an acute exacerbation and also showed no signs of acute heart failure in ECG and echocardiography. Nineteen of the patients were ex-smokers and seven were current smokers. Smoking was not allowed within 4 h before tests. All patients took inhaled β_2-adrenoceptor agonists, 15 oral corticosteroids (nine of them in combination with inhaled steroids), 13 inhaled corticosteroids only and 12 theophylline. Medication was not withdrawn before tests, however, in case of ongoing LTOT (n=7 patients), oxygen delivery was discontinued for at least 30 min prior to the tests. Baseline values of blood gases and diffusing capacity were determined in the absence of supplemental oxygen inhalation.

Table 1. Patients' characteristics

	Mean	Range
Age (years)	67±7·16	50–79
Body mass index	25·1±4·43	16–34
FEV_1 % (pred)	33·5±11·0	15–58
FEV_1 VC (%)	43·4±11·7	30–66
RV (% pred)	207·6±53·1	106–320
DL_{CO} (% pred) (n=20)	55·8±27·4	20–92
PaO_2 (mmHg)	58·4±7·31	46–70
$PaCO_2$ (mmHg)	45·4±6·69	36–60
Pack-years	51±30	5–150

All measurements were performed at rest and included determinations of PaO_2, $PaCO_2$ and oxygen saturation (SaO_2). Patients inhaled clean air (free of nitric oxide), O_2 (FiO_2), 0·29, 5 ppm NO, 5 ppm NO+O_2, 10 ppm NO and again clean air, in consecutive order. Each period of inhalation lasted 10 min. The order of inhalations was not randomized owing to technical reasons, in particular the long response time of the NO analyser used. To assess whether the sequence of inhalations would have induced a trend that could mistakenly be interpreted as an effect of inhalations, the clean air inhalation was repeated at the end of the sequence. Inhalations were performed via a mouthpiece, while patients had their nose clipped and were seated. If PaO_2 was judged too low during inhalation of 5 ppm NO, the NO concentration was not further increased to 10 ppm. At the end of each inhalation period, blood gases were measured from hyperaemic capillary earlobe blood, which has been demonstrated to produce reliable results under resting conditions (13). Earlobe blood was arterialized by application of an irritant cream 10 min prior to each test (Finalgon®, Boehringer–Ingelheim, Germany). After each earlobe puncture, the cream was applied again. SaO_2 was measured continuously (Nellcor Symphonie N-3000; Nellcor-Bennett, Pleasanton, CA, U.S.A.) and data were fed into a personal computer. For analysis of SaO_2, the average value over the last 5 min of each 10 min inhalation period was computed.

To assess the potential influence of body position, we studied the combined inhalation of O_2 and NO in both sitting and supine position in eight patients (mean PaO_2, 55·7 ±5·3 mmHg; range, 47–63 mmHg; FEV_1 25·6 ±7·4% predicted). Patients inhaled clean air, O_2 (FiO_2, 0·29), 5 ppm NO and 5 ppm NO+O_2 via a mouthpiece with clipped nose, in consecutive order. Again, the duration of inhalation periods was 10 min, and capillary blood gas analysis was performed after each of them. SaO_2 was determined as described above. Measurements in sitting and supine position were performed in random order on the same day but at least 30 min apart.

The study was approved by the Ethics Committee of the Chamber of Physicians of Schleswig–Holstein; all patients gave their informed consent.

Nitric oxide inhalation

NO was delivered through a non-rebreathing circuit from a stock tank containing 450 ppm NO in nitrogen (Linde AG, Hamburg, Germany). The gas mixture was prepared at a rate of 20 l min^{-1} in a plastic bag from clean air, O_2 and NO at the inlet of a two-way valve connected to the mouthpiece. The air not inhaled by the subjects was removed through a bypass. Throughout the study, oxygen was given at a fixed final fractional concentration of 0·29 FiO_2 within a maximal error of $\pm$0·005, which was equivalent to the additional inhalation of 1 ($\pm$0·006) l min^{-1} O_2 at a ventilation rate of about 12 l min^{-1}. The concentrations of inspired NO and NO_2 were monitored continuously by a chemoluminescence nitric oxide analyser (Monitor Labs 8840; Monitor Labs, Gibsonia, PA, U.S.A.) which was calibrated daily using 5 ppm NO calibration gas (Linde AG). The concentration of O_2 was assessed by an oxygen analyzer (O_2-Test, Jaeger, Höchberg, Germany). Ventilation was measured in the expiratory branch of the breathing system using a pneumotachograph.

Data analysis

The analysis was performed in terms of PaO_2, $PaCO_2$, SaO_2 and ventilation rate. The mean of the two values obtained after clean air inhalation at the beginning and the end of the test was taken as baseline value of each test. The effects produced during the various NO and O_2 inhalation periods were then expressed as differences against this baseline value. For each individual subject, mean values over the two study days were computed as well as the corresponding standard deviations (SD); this was done for both absolute values as well as differences to baseline values. The mean value served as a measure of the individual response and the SD as a measure of intra-individual variability. Individual mean values were then averaged over the whole group of patients to obtain overall mean values for each inhalation period. Similarly, the squares (variances) of the individual standard deviations were averaged and, afterwards, the square root was taken to obtain a single SD as a measure of the average intra-individual variability. In addition, the SD between the individual mean values was computed, as an index of inter-individual variability.

Statistical comparisons between the absolute values or the effects obtained in different inhalation periods were performed by the paired *t*-test, using the individual mean values. Clean air values were compared with the 5 and 10 ppm NO values, and O_2 values with the O_2+5 ppm NO and O_2+10 ppm NO values. Furthermore, the results of the 5 and 10 ppm inhalations in the absence of supplemental O_2 were compared to each other using their differences to the clean air values. An analogous procedure was followed for the values obtained in the presence of supplemental O_2. Statistical significance was assumed for $P<0·05$. We did not introduce Bonferrroni or other corrections

Table 2. Effect of NO on PaO_2, $PaCO_2$ and SaO_2 in patients with COPD. Mean values $\pm$standard deviations are given

	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	SaO_2 (%)
n=26			
Clean air	55·0 $\pm$ 5·7	43·3 $\pm$ 6·1	91·2 $\pm$ 2·6
+5 ppm NO	54·1 $\pm$ 6·1 **	43·2 $\pm$ 6·3	90·9 $\pm$ 2·8
n=19§			
Clean air	57·3 $\pm$ 4·9	41·5 $\pm$ 4·6	92·2 $\pm$ 2·0
+ 5 ppm NO	56·5 $\pm$ 5·1 $^{++}$	41·5 $\pm$ 5·6	91·7 $\pm$ 2·3 $^{++}$
+ 10 ppm NO	54·5 $\pm$ 4·7**	41·6 $\pm$ 4·5	91·4 $\pm$ 2·0
n=26			
O_2	72·5 $\pm$ 11·4	45·0 $\pm$ 6·1	94·5 $\pm$ 1·9
5 ppm NO	70·7 $\pm$ 11·0 *	45·2 $\pm$ 7·0	94·2 $\pm$ 2·2
n=19§			
O_2	76·1 $\pm$ 11·0	43·2 $\pm$ 6·1	95·1 $\pm$ 1·6
+5 ppm NO	74·3 $\pm$ 10·3 $^{+}$	43·2 $\pm$ 6·2	94·9 $\pm$ 1·8
+10 ppm NO	72·5 $\pm$ 9·9**	42·9 $\pm$ 4·9	94·7 $\pm$ 1·9

§Subgroups of patients studied with both 5 and 10 ppm NO.

*$P<0·05$, **$P<0·01$ *vs.* clean air or oxygen, respectively; $^{+}P<0·05$, $^{++}P<0·01$ *vs.* 10 ppm NO plus clean air or O_2, respectively. Exact *P*-values are given in the text.

Each inhalation period lasted 10 min and O_2 was given at a final concentration of 29%.

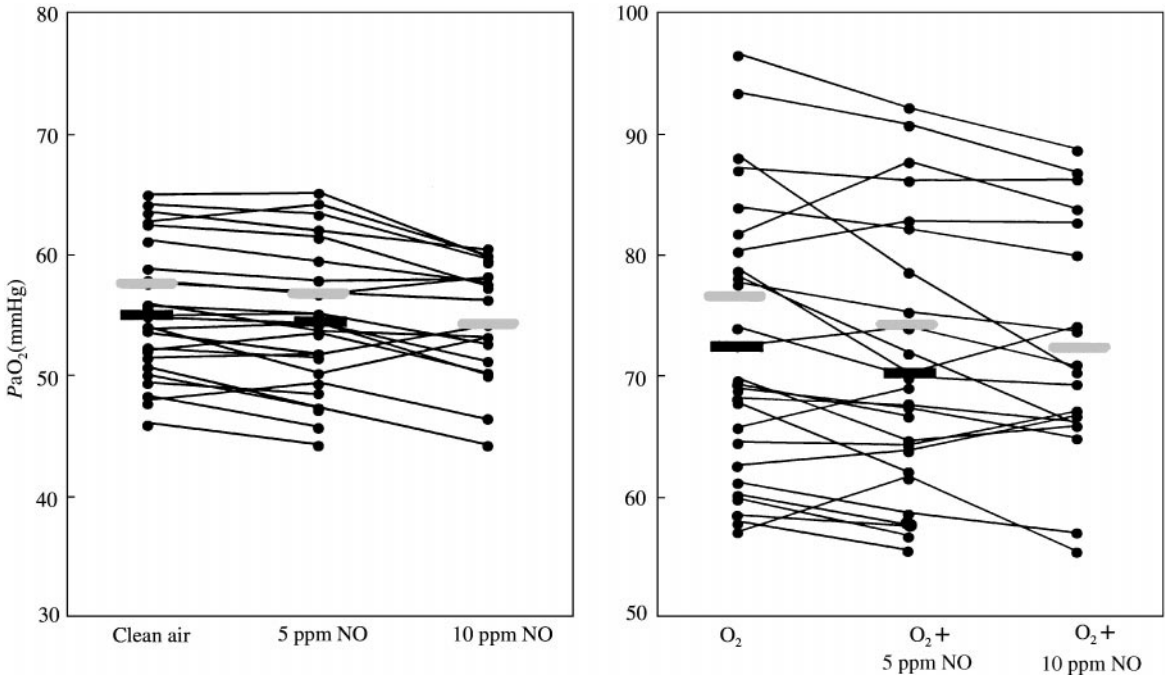

Fig. 1. Effect of nitric oxide and oxygen on PaO_2. Black bars indicate the mean values for those patients that inhaled only 5 ppm NO; grey bars indicate the mean values for those patients that inhaled 5 ppm NO and 10 ppm NO.

for multiplicity of testing, instead we gave *P*-values explicitly.

RESULTS

All of the 26 patients inhaled 5 ppm NO, and 19 patients 5 as well as 10 ppm NO. No adverse events such as headache or increasing dyspnoea occurred during the inhalation testings. Furthermore, no signs of acute right or left ventricular dysfunction were observed on the following days. The mean PaO_2 at the beginning of the inhalation periods were 55·6 mmHg and 54·5 mmHg at the beginning and the end of the inhalation procedures, respectively. Variability of PaO_2 in terms of mean intra-individual SD was 1·4 mmHg.

Effects of NO on arterial blood gases

Mean results obtained for PaO_2 and $PaCO_2$ are given in Table 2 and individual results in Fig. 1.

In the absence of supplemental oxygen, both levels of inhaled NO produced a slight but statistically significant decrease in PaO_2 as compared to clean air. The average magnitude of this decrease was 0·94 mmHg at 5 ppm NO ($P=0·002$) and 2·76 mmHg at 10 ppm NO ($P<0·0001$). These values differed significantly from each other, indicating a dose-dependent effect ($P=0·002$). Oxygen saturation showed a parallel course to that of PaO_2, although a statistically significant reduction in SaO_2 occurred only after inhalation of 10 ppm NO as compared to clean air (Table 2).

In the presence of supplemental O_2, NO also caused a significant decrease in PaO_2 as compared to the values obtained with oxygen alone. PaO_2 decreased by 1·84 mmHg at 5 ppm NO ($P=0·017$) and by 3·59 mmHg at 10 ppm NO ($P=0·007$); these two values were significantly different from each other ($P=0·026$), again indicating a dose-dependent deterioration of PaO_2. Again, SaO_2 showed a course parallel to that of PaO_2. The effects, however, were not significantly different from zero.

Both levels of inhaled NO did not cause statistically significant changes in PaO_2 as compared to baseline values (Table 2). This was true either in both the absence and presence of supplemental O_2. Owing to a technical fault, ventilation rates could not be assessed in two patients. In those patients, however, in whom ventilation rate was available ($n=24$), there were no statistically significant differences between inhalation regimes. On average ($\pm$SD), ventilation rate was 12·8 $\pm$3·21 min^{-1}.

Variability of measurements

In the absence of supplemental O_2, the average intra-individual SD of the change in PaO_2 was 2·23 mmHg after

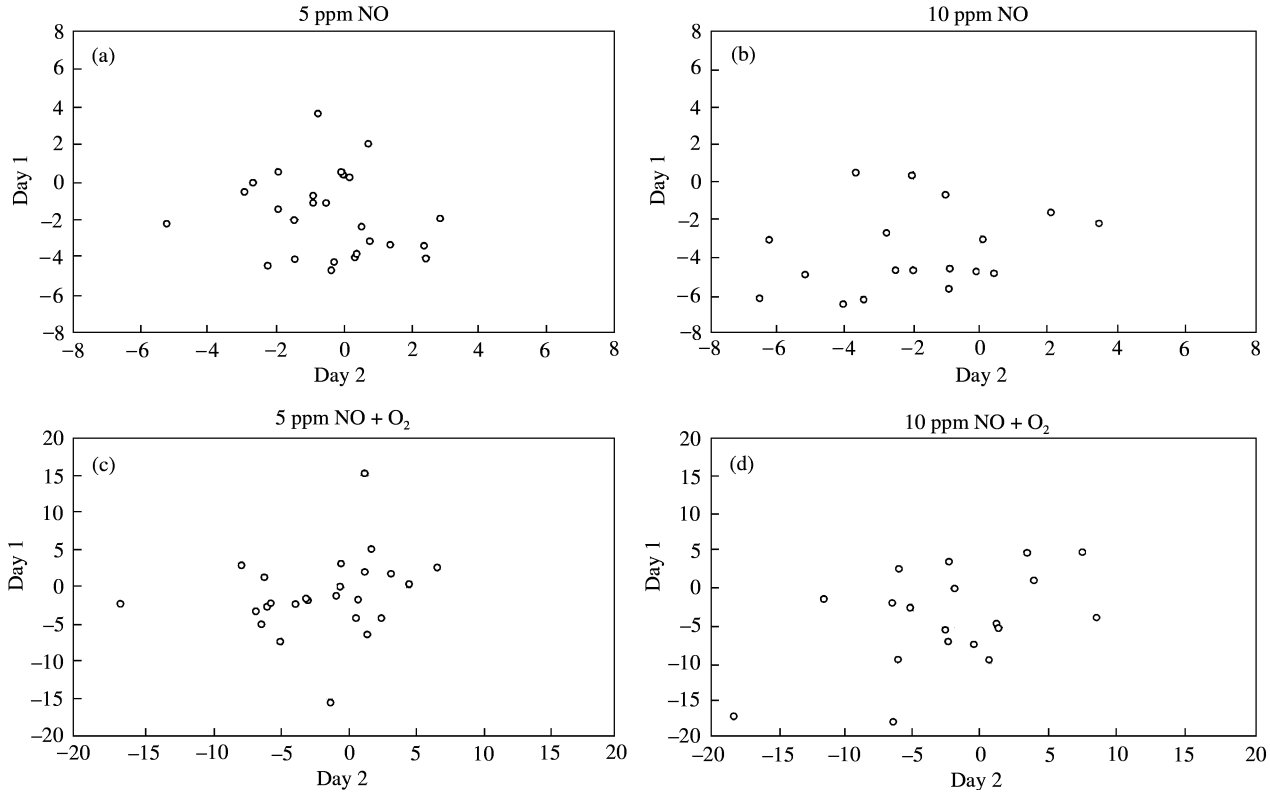

Fig. 2. Variability of the nitric oxide effects. Indicated are the differences in PaO_2 (mmHg) between 5 and 10 ppm NO *vs.* clean air (a, b) and between 5 ppm NO+O_2 and 10 ppm NO+O_2 *vs.* O_2 (c, d).

Table 3. Effect of body position on PaO_2 (mmHg) during inhalation of clean air or oxygen without or with 5 ppm NO in patients with COPD (n=8). Mean values and standard deviations are given. The changes in PaO_2 during inhalation of NO and O_2 *vs.* O_2 were statistically significant between supine and the upright position ($P < 0{\cdot}05$)

Upright position	PaO_2 (mmHg)
Clean air	55·7 ± 5·3
+5 ppm NO	55·0 ± 8·4
O_2	75·3 ± 12·5
+5 ppm NO	71·6 ± 10·8
Supine position	**PaO_2 (mmHg)**
Clean air	56·1 ± 4·6
+5 ppm NO	55·1 ± 6·7
O_2	73·5 ± 9·5
+5 ppm NO	74·6 ± 7·9

inhalation of 5 ppm NO and 2·23 mmHg after 10 ppm NO. In the presence of supplemental O_2, corresponding SD values were 4·65 and 5·33 mmHg, respectively. To illustrate the relationship between the size of the effect and its variability, Fig. 2 shows the effects obtained on the two study days plotted against each other.

Upright versus supine position

Eight patients were tested in both upright and supine position. In the absence of supplemental O_2, the measurements performed in upright position showed no statistically significant fall in PaO_2 during breathing of 5 ppm NO as compared to clean air (Table 3). The same was true for the measurements supine in position. When 5 ppm NO plus oxygen were inhaled in supine position, mean PaO_2 decreased by 3.73 mmHg (NS) as compared to oxygen alone. In the upright position, there was a mean rise in PaO_2 by 1·10 mmHg (NS). The difference between both changes was on average 4·83 mmHg and significantly different from zero ($P < 0{\cdot}05$) (Fig. 3).

DISCUSSION

The inhalation of NO has been introduced as a potential means to reduce pulmonary artery pressure and to im-

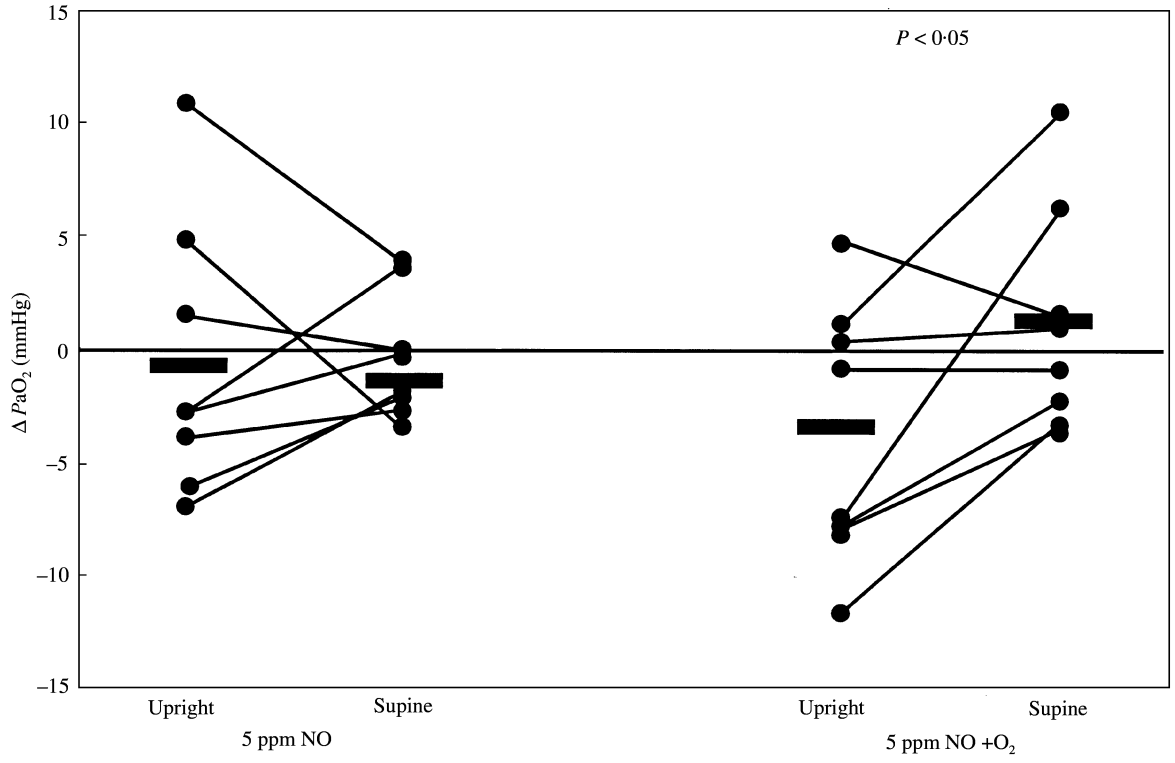

Fig. 3. Effect of body position on PaO_2. Indicated are the differences in PaO_2 between inhalation of NO and clean air (left side) and between $NO+O_2$ and O_2 (right side). The data showed a significant increase in PaO_2 between supine and upright position during breathing of NO and oxygen. Bars indicate mean values.

prove oxygenation in a number of diseases including primary pulmonary hypertension (5), ARDS (4) and COPD (6,14,15). It has been used particularly in ARDS, although recent controlled studies failed to demonstrate a beneficial effect in terms of survival rates (16–18).

In patients with severe COPD chronic hypoxaemia is a major cause for the impairment in the quality of life, survival time and exercise tolerance (19). One study demonstrated an annual increase in pulmonary artery pressure (PAP) of 1·5 mmHg in patients with COPD (20), whereas supplemental oxygen therapy was capable to invert this into an annual decrease by as much as 2·2 mmHg per year. In accordance with these results, long-term survival rates were found to be significantly improved by LTOT in patients with severe COPD (21,22). However in patients with less severe disease LTOT may have no effect (23).

One of the major causes of hypoxaemia in COPD is thought to be the ventilation–perfusion mismatch as indicated, e.g. by the multiple inert gas elimination technique (7). Vasodilators might deteriorate gas exchange in patients with COPD; indeed, Barberà *et al*. found a decrease in PaO_2 when patients breathed NO at rest (8). In contrast, exercise leads to an increase in PaO_2 during breathing of NO (24), probably because NO is preferentially diverted to alveolar units with shorter time constants, hence facilitating NO delivery to more preserved ventilation–perfusion ratios. This would optimize pulmonary blood flow and therefore better ventilation and perfusion balance, other things being equal. During exercise the inhaled NO might be delivered to the well-ventilated and well-perfused compartments preferentially, whereas under resting conditions it also might act in poorly ventilated and/or perfused compartments. This raises the possibility that simultaneous delivery of oxygen may reverse a detrimental effect of NO under resting conditions.

A number of authors have investigated the effect of combined inhalation of NO and O_2 in spontaneously breathing patients with moderate to severe COPD. Yoshida *et al*. (9) found a significant increase in PaO_2 of 20·1 mmHg and a decrease in pulmonary artery pressure of 1·7 mmHg during breathing of 2 ppm NO plus O_2 as compared to O_2 alone. The mean PaO_2 of the patients enrolled in this study was 72·3 mmHg, although baseline FEV_1 was similar to that of patients enrolled in the present study. A similar result has been reported by German *et al*. (10) in patients with more severe COPD ($PaO_2 < 60$ mmHg and mean FEV_1 33·5% predicted). Despite the beneficial effects observed on average, the authors also observed a large variability

in individual responses. Some patients demonstrated a marked improvement in PaO_2 when NO was added to oxygen, whereas others remained stable or even showed a slight decrease in PaO_2 values. Recently published data by Ashutosh *et al*. (25) demonstrated that in patients with severe COPD a 24-h inhalation of NO and O_2 resulted in a significant increase in cardiac output and a decrease in pulmonary vascular resistance as compared to LTOT alone. Noteworthy enough, however, PaO_2 remained unchanged. Similar results were found in patients with exacerbation of COPD under mechanical ventilation (26).

It might be argued that the differences between our data and the previous results could be due to the fact that patients inhaled NO via mouthpiece and not via face mask or nasal cannula. However this approach was chosen to administer well-defined NO concentrations independently from the patient's breathing pattern and we consider it unlikely that this procedure significantly affected PaO_2 levels. The whole sequence of measurements was performed under stable conditions as indicated by the fact that PaO_2 values obtained at the beginning and the end of each test, when patients were breathing clean air, were very similar.

It is well known that both ventilation and perfusion of the lung depend on body position. Therefore, it is not *a priori* guaranteed that the results obtained in supine position are also true for upright position. When subjects were in upright position, the inhalation of 5 ppm NO plus oxygen led to a deterioration in PaO_2. However, when subjects changed their position to supine, PaO_2 slightly increased during inhalation of 5 ppm NO plus O_2 as compared to O_2 alone. The concentration of 5 ppm NO was selected as it had been found previously beneficial when given in semi-recumbent position (10). Although the individual effects were not statistically significant but only the difference between those obtained for both positions, the result might at least partially explain the discrepancy between our and the previous data (9, 10). They suggest that a redistribution of ventilation and perfusion occurred in upright as compared to supine body position. However, the data must be interpreted cautiously owing to the large variability of responses. Lung volume and/or cardiac function (27) may have influenced the response to inhaled NO, as shown by previous authors in ARDS or ventilated patients. However, the mechanism of these pathophysiological changes remains unsettled, as we did not measure these parameters.

Previous data indicating large differences in response between subjects did not allow to define responders and non-responders through the reproducibility of responses. To accomplish this, we performed repeated measurements in the same subjects. As a result, the variability was too large to allow a clear-cut definition of 'responders' even for the detrimental effect observed on average for upright position. It seems that a potential therapeutic application of inhaled NO requires (1) that there is a certain percentage of patients with beneficial effects and (2) that the effect is relatively independent from the NO concentration, owing to the difficult to achieve a constant concentration under varying breathing conditions.

In summary, our data indicate that in patients with moderate to severe COPD inhalation of NO with and without supplemental oxygen leads to a decrease in PaO_2 when patients are in upright position. These changes in PaO_2 were small, but nevertheless indicate no improvement.

Furthermore, the intra-individual variability of the responses is large and of similar magnitude as the average effect. We conclude that treatment with inhaled NO with or without supplemental oxygen is not a promising therapeutic approach to ameliorate hypoxaemia in patients with COPD.

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